Restriction of placental and fetal growth in sheep alters fetal blood pressure responses to angiotensin II and captopril

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1. We have measured arterial blood pressure between 115 and 145 days gestation in normally grown fetal sheep (control group; $n = 16$) and in fetal sheep in which growth was restricted by experimental restriction of placental growth and development (PR group; $n = 13$). There was no significant difference in the mean gestational arterial blood pressure between the PR ($42{\cdot}7 \pm 2{\cdot}6$ mmHg) and control groups ($37{\cdot}7 \pm 2{\cdot}3$ mmHg). Mean arterial blood pressure and arterial P_{O_2} were significantly correlated in control animals ($r = 0{\cdot}53$, $P < 0{\cdot}05$, $n = 16$), but not in the PR group.

2. There were no changes in mean arterial blood pressure in either the PR or control groups in response to captopril ($7{\cdot}5$ μg captopril min^{-1}; PR group $n = 7$, control group $n = 6$) between 115 and 125 days gestation. After 135 days gestation, there was a significant decrease ($P < 0{\cdot}05$) in the fetal arterial blood pressure in the PR group but not in the control group during the captopril infusion (15 μg captopril min^{-1}; PR group $n = 7$, control group $n = 6$).

3. There was a significant effect ($F = 14{\cdot}75$; $P < 0{\cdot}001$) of increasing doses of angiotensin II on fetal diastolic blood pressure in the PR and control groups. The effects of angiotensin II were different ($F = 8{\cdot}67$; $P < 0{\cdot}05$) in the PR and control groups at both gestational age ranges.

4. These data indicate that arterial blood pressure may be maintained by different mechanisms in growth restricted fetuses and normally grown counterparts and suggests a role for the fetal renin–angiotensin system in the maintenance of blood pressure in growth restricted fetuses.

A series of epidemiological studies have described a relationship between low birth weight and high blood pressure in adult life and have proposed that factors associated with restriction of growth *in utero* act to reprogramme the development of the cardiovascular system which leads to the emergence of hypertension in adult life (Barker *et al.* 1990; Barker, 1992). It has also been demonstrated in pregnant rats that maternal protein restriction results in high blood pressure in the growth restricted offspring (Langley & Jackson, 1994). Interestingly, in these experiments treatment of the offspring for a 3 week period with the angiotensin converting enzyme (ACE) inhibitor captopril normalized the blood pressure (Langley-Evans & Jackson, 1995). These studies in the postnatal rat provide clear evidence that the renin–angiotensin system is important in the maintenance of hypertension in the offspring after maternal nutrient restriction during pregnancy. It is unknown, however, whether growth restriction *in utero* is associated with changes in the role of the renin–angiotensin system in the regulation of arterial blood pressure before birth. A model of experimental restriction of placental growth and function which results in fetal hypoxaemia, hypoglycaemia and growth restriction has been previously described (Robinson *et al.* 1979, 1980). In the present study we have also investigated the effects of experimental restriction of placental growth and function, and hence fetal growth, on fetal arterial blood pressure during late gestation and we have infused captopril to determine the role of the endogenous renin–angiotensin system in the maintenance of blood pressure in the growth restricted fetus. We have also investigated the effects of placental restriction on the blood pressure responses of the growth restricted fetus to increasing doses of angiotensin II (AII).

METHODS

Animals and surgery

All procedures were approved by The University of Adelaide Animal Ethics Committee. Thirty-three pregnant Border × Leicester cross Merino ewes were used in this study. In 14 ewes (placental restriction group; PR), the majority of endometrial caruncles were removed from the uterus prior to conception as previously described (Robinson *et al.* 1979). This procedure restricts the number of placental cotyledons which are formed subsequently limiting placental and hence fetal growth (Robinson *et al.* 1979). All surgery was performed under aseptic conditions with general anaesthesia induced by an intravenous injection of sodium thiopentone ($1{\cdot}25$ g ml^{-1}, Boehringer Ingelheim, NSW, Australia) and

maintained with 3–4% halothane in oxygen. The ewes were kept under observation for 4–7 days post-surgery before being returned to the farm. After a minimum of 10 weeks recovery post-surgery, the ewes entered a mating programme and pregnancies were confirmed by ultrasound at approximately 60 days gestation.

In all ewes (PR $n = 14$, control $n = 19$), vascular catheters were implanted in a fetal and maternal carotid artery and jugular vein and amniotic cavity between 105 and 124 days gestation (term = 147 ± 3 days gestation). All catheters were filled with heparinized saline and the fetal catheters exteriorized through an incision made in the ewe's flank. All ewes and fetal sheep received a 2 ml intramuscular injection of antibiotics (procaine penicillin, 250 mg ml^{-1}; dihydrostreptomycin, 250 mg ml^{-1}; procaine hydrochloride, 20 mg ml^{-1}; Lyppards, Adelaide, Australia) at the time of surgery. The ewes were housed in individual pens in animal holding rooms with a 12 h light–dark cycle and fed once daily between 09.00 h and 13.00 h with water *ad libitum*. Fetal arterial blood samples (0·5 ml) were collected throughout late gestation, from all fetuses (PR $n = 103$ samples, control $n = 128$ samples) in order to determine pH, P_{O_2}, P_{CO_2}, oxygen saturation and haemoglobin content using an ABL 520 analyser (Radiometer, Copenhagen, Denmark). Arterial oxygen content per 100 ml blood was calculated as follows:

$$O_2 \text{ content} = (P_{O_2} \times 0{\cdot}003) + [\text{Hb}] \times (O_2 \text{ saturation}/100) \times 1{\cdot}39,$$

where P_{O_2} represents arterial partial pressure of oxygen and [Hb] represents haemoglobin concentration in grams per decilitre. Animals were allowed to recover from surgery for at least 4 days prior to experimentation.

Arterial blood pressure measurements

Fetal arterial blood pressure (BP) and intra-amniotic pressure were measured directly from the fetal carotid arterial catheter and amniotic catheter, respectively. The catheters were connected to a MacLab data acquisition system via a MacLab 1050 displacement transducer and quad-bridge amplifier (ADInstruments, Castle Hill, NSW, Australia), and arterial blood pressure, corrected for amniotic pressure, was measured using the MacLab Chart software on a Power Macintosh computer. Baseline arterial BP was recorded for periods up to 60 min before each experiment.

Captopril infusion

Captopril ([25]-1-[3-mercapto-2-methylpropionyl]-L-proline, Sigma Chemical Co.) was infused intravenously for 4 h (Graseby Medical syringe driver M5-10A, Selby Scientific & Medical, Gold Coast, Queensland, Australia) at between 115 and 125 days gestation (7·5 μg captopril min^{-1}; PR group $n = 7$, control group $n = 6$) and between 135 and 145 days gestation (15 μg captopril min^{-1}; PR group $n = 7$, control group $n = 6$). In these experiments, captopril was administered at both gestational age ranges in five fetuses in the PR group and in four fetuses in the control group.

In control experiments, intravenous saline (3 ml, 4h) was infused between 130 and 135 days gestation (PR group $n = 5$, control group $n = 5$). Fetal arterial BP and intra-amniotic pressure measurements were recorded continuously between 60 min before and 180 min after the end of the infusion.

Angiotensin II

Bolus intravenous doses of AII (0·2, 0·75, 1·5, 3·0, 5·0 and 10·0 μg, Peninsula Laboratories Inc., Belmont, CA, USA) were administered in a random order every 20 min in a 2 h period between 115 and 125 days gestation (PR group $n = 4$, control group $n = 4$) and similarly between 135 and 145 days gestation (PR group $n = 5$, control group $n = 4$). The doses of AII relative to fetal body weight (μg kg^{-1}) were calculated for each experiment using growth curves established in this laboratory for 74 control and 64 PR fetal sheep. The growth curve of the control fetuses was best described by the polynomial equation:

$$\text{Fetal weight} = 0{\cdot}0008 \times \text{gestational age}^2 - 0{\cdot}1046 \times \text{gestational age} + 3{\cdot}6508,$$

where fetal weight is in kilograms and gestational age is in days ($r = 0{\cdot}94$, $n = 74$). The growth curve for PR fetuses was described by the exponential equation:

$$\text{Fetal weight} = 0{\cdot}556e^{0{\cdot}0284 \times \text{ gestational age}}$$

($r = 0{\cdot}72$, $n = 64$). Fetal arterial BP and intra-amniotic pressure were measured continuously throughout the AII dose–response experiment. In these experiments, AII was administered at both gestational age ranges to three fetuses in the PR group and to three fetuses in the control group.

Autopsy

All ewes and fetuses were killed with an overdose of sodium pentobarbitone (Lyppards, Castle Hill, NSW, Australia) at 145 days gestation and fetal sheep were delivered by hysterotomy, weighed and decapitated.

Statistical analysis

Data are shown as means ± standard error of the mean. The mean fetal arterial P_{O_2} was calculated for each fetus as the average of all arterial P_{O_2} values obtained between 115 and 145 days gestation. A mean arterial BP was calculated for each of 16 control and 13 PR fetal sheep. This was calculated from the mean basal systolic and diastolic blood pressure measurements taken over a 2 min period before administration of either AII or captopril. There were four values available for each sheep fetus across the gestational age range of the study and the average of these values was used. Fetal body weights and mean arterial P_{O_2} and blood pressure were compared in the control and PR groups using Student's unpaired t test. Correlations between fetal weight, P_{O_2} and arterial BP were determined using linear regression analysis.

The maximal arterial BP response (defined as the maximum blood pressure value achieved after each given dose of AII) and the change in BP from baseline (the difference between the maximal BP response to AII and the mean arterial BP measured in the 2 min preceding administration of the first AII dose) in response to AII were analysed using a multifactorial ANOVA with repeated measures using the Statistical Package for Social Sciences (SPSSX, Chicago, IL, USA) on a Vax mainframe computer. Specified factors for the BP analysis included group (PR *vs.* control), AII dose (0·01–4·0 μg kg^{-1}), gestational age (< 125 days *vs.* > 135 days) and animal. Similarly, fetal arterial BP responses to captopril were also analysed using multifactorial ANOVA. When a significant interaction between major factors was identified by ANOVA, the data were split on the basis of the interacting factor and reanalysed. Duncan's new multiple range test was used post-ANOVA to identify significant differences between mean values, and a probability level of 5% ($P < 0{\cdot}05$) was taken as significant.

RESULTS

Fetal outcome and arterial blood gas status

Fetal body weights at post-mortem were significantly reduced ($P < 0{\cdot}05$) in the PR group (2·73 ± 0·3 kg) when compared with the control group (5·14 ± 0·2 kg). There were also significant differences between the PR and control groups in the mean levels of fetal arterial P_{O_2}, O_2 saturation

Table 1. Restriction of placental function and fetal arterial blood gas status

	P_{O_2} (mmHg)	O_2 saturation (%)	pH	P_{CO_2} (mmHg)	Hb level (g dl^{-1})	O_2 content (ml dl^{-1})
PR ($n = 14$)	15·4 ± 0·9*	45·2 ± 2·7*	7·34 ± 0·01	48·9 ± 0·4	10·7 ± 0·6	6·6 ± 0·3*
Control ($n = 19$)	21·9 ± 0·6	67·1 ± 2·2	7·4 ± 0·01	44·5 ± 0·7	9·6 ± 0·3	8·8 ± 0·2

Values are means ± S.E.M. and the asterisks denote mean values in the PR group which are signficantly different ($P < 0·05$) from control values.

and O_2 content (Table 1). When the two groups were combined, there was a significant correlation ($r = 0·79$, $P < 0·05$; fetal weight = $0·24 \times P_{O_2} - 0·46$) between the mean gestational arterial P_{O_2} and fetal body weight at 145 days gestation.

Placental restriction and fetal arterial BP

There was no significant difference in mean basal arterial BP between the PR and control groups (42·7 ± 2·6 mmHg and 37·7 ± 2·3 mmHg, respectively). There was a significant correlation between mean arterial BP and P_{O_2} in control animals ($r = 0·53$, $P < 0·05$, $n = 16$), which was not present, however, in the PR group ($n = 13$; Fig. 1).

Captopril infusion

There was no significant effect of captopril on fetal arterial BP before 125 days gestation in either the PR or control groups. After 135 days gestation, there was a significant interaction between the effects of captopril on the systolic BP ($F = 1·58$, $P < 0·05$), diastolic BP ($F = 1·73$, $P < 0·05$) and the mean arterial BP ($F = 1·76$, $P < 0·05$) in the PR and control groups with time. In the PR group, there was a significant decrease in the mean arterial BP by 120 min after the start of the infusion (−7·4 ± 1·2 mmHg) compared with the control period of the PR group, and the mean arterial BP remained low throughout the remainder of the infusion period (Fig. 2). In the control group, however, there was no significant change in the mean arterial BP throughout

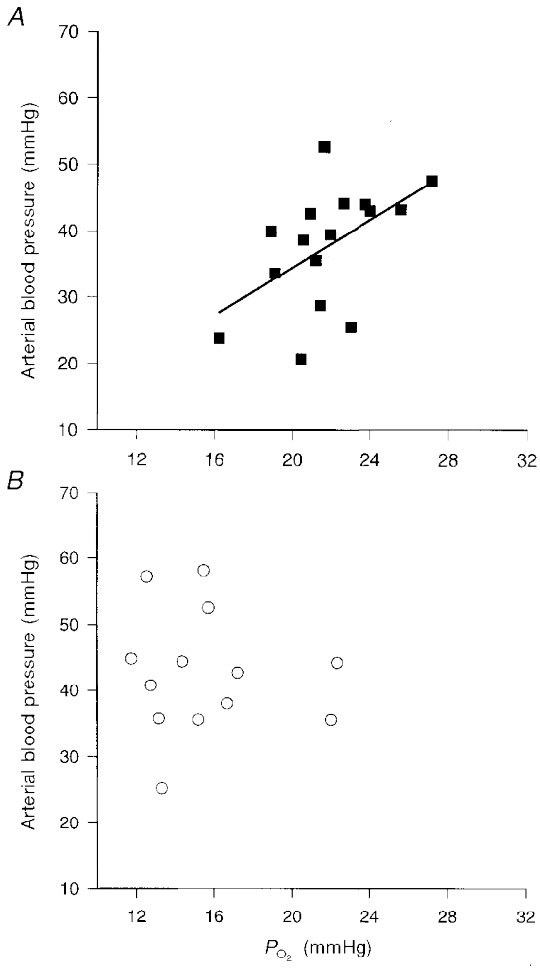

Figure 1. The relationship between arterial P_{O_2} and mean arterial blood pressure in control and PR fetal sheep

The relationship between the mean gestational arterial P_{O_2} values and mean arterial blood pressure in control fetal sheep (■, $n = 16$; *A*) and PR fetal sheep (○, $n = 13$; *B*). There was a significant correlation between arterial P_{O_2} and blood pressure in the control fetal sheep ($r = 0·53$, $P < 0·05$).

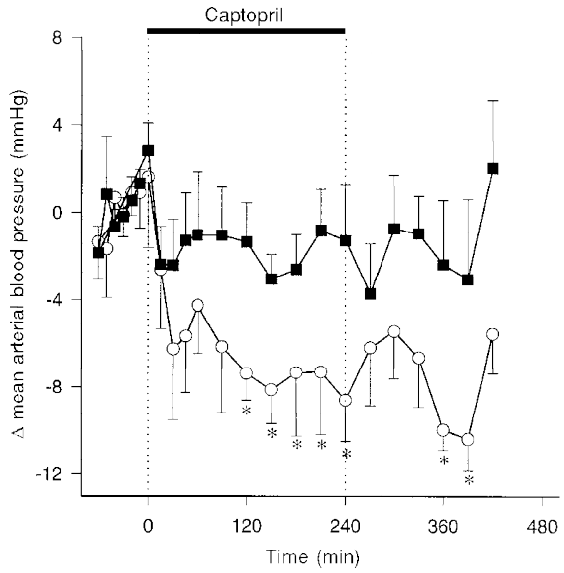

Figure 2. The effect of captopril on mean arterial blood pressure in control and PR fetal sheep
The arterial blood pressure response (mean ± S.E.M.) to a 4 h captopril infusion (15 μg min^{-1}) in control fetuses (■, $n = 6$) and PR fetuses (○, $n = 7$) between 135 and 145 days gestation. * $P < 0{\cdot}05$, significantly different from pre-infusion values.

the captopril infusion or during the recovery period (Fig. 2). There was no relationship between the diastolic BP response to captopril and the dose of captopril infused when expressed as micrograms captopril per kilogram fetal weight. There were no changes in mean arterial BP in either the PR or control groups during or after intrafetal infusion of saline.

Fetal arterial BP responses to angiotensin II

There was a significant effect ($F = 14{\cdot}75$, $P < 0{\cdot}001$) of increasing doses of AII on fetal diastolic BP in the PR and control groups. There was a significant interaction ($F = 8{\cdot}67$, $P < 0{\cdot}05$), however, between the effects of AII in the PR and control groups which was present in both gestational age groups. In the PR group, there were no differences between the gestational groups in the maximal diastolic BP responses to increasing doses of AII and therefore these responses were pooled. In the PR group, fetal diastolic BP increased significantly after administration of the lowest dose of AII (0·04 μg kg^{-1}) and increased progressively with increasing doses of AII to reach a maximal response at doses of AII between 1 and 4 μg kg^{-1} (Fig. 3). In the control group, there were also no differences in the maximal diastolic BP responses to AII between the gestational age groups and, again, these responses were pooled. In this group, whilst the fetal diastolic BP increased significantly after administration of 0·04 μg AII kg^{-1}, there was no

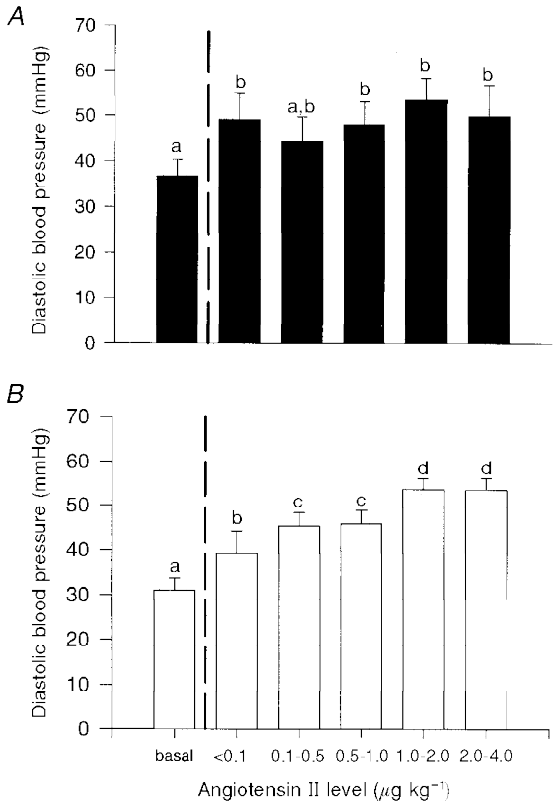

Figure 3. The effect of angiotensin II on diastolic blood pressure in control and PR fetal sheep
The diastolic blood pressure response (means ± S.E.M.) to increasing bolus doses of AII (0·01–4·0 μg kg^{-1}) in control fetal sheep ($n = 8$; black histograms; *A*) and PR fetal sheep ($n = 9$; open histograms; *B*) between 115 and 145 days gestation. Different letters denote significant differences ($P < 0{\cdot}05$) between mean values.

Table 2. The effect of angiotensin II on systolic blood pressure in PR and control fetal sheep

Dose (μg kg^{-1})	Systolic BP PR (mmHg)	Systolic BP Control (mmHg)
Baseline	53·9 ± 3·0 [a]	56·4 ± 2·8 [a]
0·01–0·10	62·9 ± 4·1 [b]	63·6 ± 3·2 [b]
0·11–0·50	63·8 ± 2·8 [b,c]	66·2 ± 3·6 [b,c]
0·51–1·0	69·7 ± 2·8 [c]	71·2 ± 4·7 [c]
1·1–2·0	85·1 ± 3·4 [d]	75·0 ± 8·3 [d]
2·1–4·0	83·8 ± 3·7 [d]	82·0 ± 8·5 [d]

Values are means ± S.E.M. and different superscripts denote significant differences ($P < 0·05$) between the mean systolic blood pressure responses to increasing doses of AII within the groups.

further increase in the maximal diastolic BP in response to increasing doses of AII (Fig. 3).

There were no differences between the PR and control groups in the systolic BP responses to increasing doses of AII at either gestational age range (Table 2).

DISCUSSION

We have used a model of restriction of placental growth and function to investigate the impact of a suboptimal intrauterine environment on the regulation of arterial BP by the renin–angiotensin system. Fetuses in the placentally restricted group were chronically hypoxaemic and significantly growth restricted when compared with fetuses from the control group and there was a significant relationship between mean gestational P_{O_2} and fetal weight across both fetal groups. There was a significant and direct relationship between mean arterial BP and P_{O_2} in normally grown fetal sheep in late gestation, which was not present in growth restricted fetal sheep. The suppression of arterial BP by the ACE inhibitor captopril only in the growth restricted group suggests that the renin–angiotensin system plays a greater role in the maintenance of arterial BP in the growth restricted fetal sheep than in normally grown fetuses. Finally, there were also differences between normally grown and growth restricted fetal sheep in the diastolic BP responses to increasing doses of AII.

Mean arterial BP

Whilst we found that there was no difference in the mean arterial BP between normally grown and growth restricted fetal sheep, we found that there was a positive relationship between BP and the mean gestational P_{O_2} in control animals which was not present in the placentally restricted group. Given that the fetal sheep with higher mean gestational arterial P_{O_2} values are also larger, it is possible that the higher mean arterial BP values in the normally grown fetal sheep reflect an increased cardiac output. An alternative possibility is that as the fetus grows fetal vascularity does not increase in parallel with fetal size, which would result in an increased fetal peripheral vascular resistance and arterial BP.

A previous study by Daniel *et al.* (1996) also found a positive correlation between arterial BP and the fetal : maternal weight ratio in a combined group of control fetuses and fetal sheep, in which mild growth restriction and hypoxaemia was produced by withdrawal of 25 ml day^{-1} of maternal blood throughout the second half of pregnancy. These authors concluded that fetal hypotension may be a good indicator of growth restriction. Given the results of our present study, however, we would suggest that the direct relationship between arterial BP and arterial P_{O_2} does not hold in moderately or severely growth restricted fetuses.

Three previous studies have also reported no differences in mean arterial blood pressure between normally grown fetal sheep and fetal sheep which were chronically hypoxaemic and growth restricted after either restriction of placental growth or embolization of the uteroplacental vascular bed in late gestation (Llanos *et al.* 1980; Robinson *et al.* 1983; Walker *et al.* 1990). Murotsuki *et al.* (1997) have reported, however, that there was a significant increase in fetal blood pressure in response to a 21 day period of embolization of the fetal placental circulation. These studies did not examine, however, whether there were any differences in the relationship between fetal arterial BP and P_{O_2} in growth restricted and normally grown fetuses across late gestation. Whilst the fetal cardiovascular responses to acute episodes of hypoxaemia lasting several hours or less have been well documented (Boddy *et al.* 1974; Cohn *et al.* 1974; Jensen *et al.* 1987; Yaffe *et al.* 1987; Jansen *et al.* 1989; Giussani *et al.* 1993), there is relatively little information on fetal cardiovascular responses to the imposition of chronic hypoxaemia, i.e. periods of hypoxaemia which extend across weeks or months. It is possible that the loss of the relationship between arterial BP and P_{O_2} in the placentally restricted fetuses is a consequence of a reduction in arteriolar branching in key fetal circulatory regions due to an adverse effect of chronic hypoxaemia on angiogenesis. Alternatively the loss of this relationship may be a consequence of an increase in the circulating concentrations or actions of vasoactive hormones which are secreted in response to the decrease in fetal oxygenation and nutrient status. The key hormones include noradrenaline (Simonetta *et al.* 1997), cortisol (Phillips *et al.* 1996) and angiotensin II.

Captopril

Fetal arterial BP did not change during or after infusion of the ACE inhibitor captopril in normally grown fetal sheep during the last 30 days of gestation. This indicates that the renin–angiotensin system is not acting to maintain basal arterial BP in these animals. There are previous studies which have found a change in arterial BP after administration of captopril in normally grown fetal sheep and a role for AII in the maintenance of vascular tone in the fetal peripheral and renal circulations has been suggested (Iwamoto & Rudolph, 1979; Robillard *et al.* 1983; Lumbers

et al. 1992). Green *et al.* (1998), however, have reported a lack of effect of captopril infusion on femoral blood flow in healthy fetal sheep under normoxic conditions. These authors concluded that circulating AII does not contribute to cardiovascular control during normoxic conditions in healthy fetuses (Green *et al.* 1998).

In the present study, we found that captopril had no effect on arterial BP in the PR group before 125 days gestation. After 135 days gestation, however, infusion of captopril significantly decreased arterial BP in these fetuses and this effect was unrelated to the degree of growth restriction in this group. Our results therefore suggest that the renin–angiotensin system plays a greater role in the regulation of arterial BP in the placentally restricted than in the normally grown fetal sheep in late gestation. One possibility is that there is an increase in circulating AII concentrations in late gestation as a consequence of the chronic hypoxaemia present in the placentally restricted group. Whilst fetal AII concentrations are elevated during acute periods of hypoxaemia (Broughton Pipkin *et al.* 1974; Robillard *et al.* 1981; Gomez & Robillard, 1984; Tomita *et al.* 1985; Green *et al.* 1998), captopril infusion does not alter the mean arterial BP and peripheral blood flow changes during a 60 min period of fetal hypoxaemia (Green *et al.* 1998). Captopril infusion did, however, blunt the hypertensive response and attenuate the fall in femoral blood flow in response to hypoxia in fetal sheep in which the carotid sinus nerves were cut (Green *et al.* 1998). Thus, once the carotid chemoreflex mechanisms were removed, there was a significant role for AII in the regulation of the BP and peripheral blood flow responses to acute hypoxaemia. Similarly, plasma AII concentrations do not increase during a prolonged period (48 h) of hypoxaemia in intact fetal sheep, but do increase in response to the prolonged hypoxaemia after the carotid sinus nerves are cut (Bocking *et al.* 1988). One possibility, therefore, is that the functioning of the carotid chemoreflex mechanisms may be downregulated by the presence of a chronically low arterial P_{O_2} in the placentally restricted fetus and that a role for circulating AII in the long term regulation of mean arterial BP then becomes apparent.

Angiotensin II

Increasing doses of AII resulted in an increase in fetal diastolic and systolic BP in the control and growth restricted fetal sheep. This is consistent with previous studies in which changes in fetal arterial BP have been measured in response to bolus doses or short term infusions of AII in normally grown fetal sheep in late gestation (Ismay *et al.* 1979; Iwamoto & Rudolph, 1981; Tangalakis *et al.* 1992; Rosenfeld *et al.* 1995; Stevenson & Lumbers, 1995). It is unknown whether AII acts directly through binding to angiotensin receptors at peripheral or central target sites within the fetal cardiovascular system. It has been demonstrated that AII binding sites are present in the fetal sheep aorta and placental arteries (Rosenfeld *et al.* 1993) and that the two types of angiotensin receptor – AT1 and AT2 – are expressed in fetal tissues in a range of species including sheep, rat and human tissues (Lazard *et al.* 1994; Robillard *et al.* 1994, 1995; Shanmugam & Sandberg, 1996). Whilst it is clear that the AT1 receptor is important in the stimulation of vascular smooth muscle contraction in adults, the function of the AT2 receptor is less clearly defined (Timmermans *et al.* 1992; Cox *et al.* 1996).

In the present study, the diastolic BP responses to increasing doses of AII were significantly different in the normally grown and growth restricted groups. It is well established during acute hypoxaemia that blood flow to the brain, heart and adrenal glands is increased and that blood flow to the gastrointestinal, renal and peripheral vascular beds decreases (Jensen *et al.* 1987; Yaffe *et al.* 1987; Jansen *et al.* 1989; Giussani *et al.* 1993). Furthermore this redistribution of fetal cardiac output is maintained with prolonged hypoxaemia in pregnancy (Bocking *et al.* 1988; Rurak *et al.* 1990). It is possible that prolonged hypoxaemia may stimulate an increase in circulating AII concentrations as discussed above. Alternatively, factors associated with prolonged hypoxaemia may act to increase expression of the vasoactive AT1 receptor subtypes within the vascular smooth muscle and hence increase vascular responsiveness to AII. It has previously been demonstrated that cortisol infusion in normally grown fetuses enhanced the fetal arterial BP responses to increasing doses of AII but not to noradrenaline (Tangalakis *et al.* 1992). Circulating cortisol concentrations are higher in late gestation in placentally restricted than in normally grown fetal sheep (Phillips *et al.* 1996) and the glucocorticoids may act to increase AT1 receptor expression in vascular smooth muscle in specific fetal circulatory beds.

In summary, there was a significant, positive relationship between mean arterial BP and P_{O_2} in normally grown fetal sheep in late gestation, which was not present in severely growth restricted fetal sheep. The suppression of arterial BP by the ACE inhibitor captopril in the growth restricted group indicates that the renin–angiotensin system plays a greater role in the maintenance of arterial BP in the growth restricted fetal sheep than in normally grown animals. Finally, there were also differences between normally grown and growth restricted fetal sheep in the diastolic BP responses to increasing doses of AII in early and late gestation. These data indicate that arterial BP may be maintained by different mechanisms in growth restricted fetuses and normally grown counterparts. We have also presented evidence which could support a role for the fetal renin–angiotensin system in the programming of adult hypertension after growth restriction *in utero*.

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